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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,389	06/04/2001	Hermann Bujard	085449-0164	5305

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,389	BUJARD ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to a Non-Final Rejection, June 16, 2005, on September 16, 2005.

Claims 21-54 are pending.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-35, 37-54 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse, wherein:

1) the transgene comprises a transcriptional regulatory element functional in cells of the mouse operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a mutated Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which activates transcription in eukaryotic cells,

said transgene is expressed in cells of the mouse at a level sufficient to produce amounts of said fusion protein that are sufficient to activate transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the mouse, said fusion protein binds to the tet operator-linked gene and activates transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable levels, wherein the level of expression of the tet operator-linked gene can be down modulated by depleting tetracycline or a tetracycline analogue from the mouse;

2) the transgene comprises a transcriptional regulatory element functional in cells of the mouse operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a mutated Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells,

said transgene is expressed in cells of the mouse at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the mouse, said fusion protein binds to the tet operator-linked gene and inhibits transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable

levels, wherein the level of expression of the tet operator-linked gene can be up regulated by depleting tetracycline or a tetracycline analogue from the mouse; or

3) the transgene comprises a transcriptional regulatory element functional in cells of the mouse operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells,

said transgene is expressed in cells of the mouse at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the mouse, said fusion protein binds to the tet operator-linked gene and inhibitss transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable levels, wherein the level of expression of the tet operator-linked gene can be upregulated by depleting tetracycline or a tetracycline analogue from the mouse,

does not provide enablement for,

the full breadth of any transgenic non-human animal comprising a transgene integrated into the genome of the animal and a tet-operator-linked gene in the genome of the animal wherein:

1) the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a mutated Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which activates transcription in eukaryotic cells,

said transgene is expressed in cells of the animal at a level sufficient to produce amounts of said fusion protein that are sufficient to activate transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the animal, said fusion protein binds to the tet operator-linked gene and activates transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable levels, wherein the level of expression of the tet operator-linked gene can be down modulated by depleting tetracycline or a tetracycline analogue from the animal;

2) the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a mutated Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells,

said transgene is expressed in cells of the mouse at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the animal, said fusion protein binds to the tet operator-linked gene and inhibits transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable levels, wherein the level of expression of the tet operator-linked gene can be up regulated by depleting tetracycline or a tetracycline analogue from the animal; or

3) the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells,

said transgene is expressed in cells of the animal at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the animal, said fusion protein binds to the tet operator-linked gene and inhibits transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable

levels, wherein the level of expression of the tet operator-linked gene can be upregulated by depleting tetracycline or a tetracycline analogue from the animal,

for reasons of record set forth in the Office Actions of January 16, 2004, October 15, 2004, and June 16, 2005.

Claim 36 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the Office Actions of January 16, 2004, October 15, 2004, and June 16, 2005. Claim 36 is rejected for a full lack of enablement as claim 36 does not comprise any enabled elements.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in

determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Applicant's arguments pages 10-13 of Applicant's response filed September 16, 2005 have been fully considered and are persuasive in part.

The Applicant asserts in point A, page 10-11, that the claimed invention is not drawn to "phenotypes" but to transcription of the gene of interest at "detectable levels." Thus, the claimed invention does not require the transgenic animal to exhibit any particular phenotype, which is the basis of the Examiner's enablement rejection. The Examiner disagrees with the Applicant's assertion because the point of using the claimed product, a transgenic animal, is because it is a model of disease or exhibits symptoms of a disease, and therefore, these transgenic non-human animals would need to exhibit a phenotype. With regards to the Applicant's assertion that the claimed invention should be based on the fact that the claimed invention has changes in transcription levels of the gene of interest is not persuasive because there are examples in the art wherein changing the transcription levels of the gene of interest does not yield any phenotype. For example, transgenic mice that overexpress wild type human presenilin 1 (PS1) do not exhibit any pathology (Duff et al., 1996, Nature: 383, 710-713,

page 711, 1st col., 3rd parag.). For these transgenic non-human animals, there is no enabled use because an artisan would not know how to use the transgenic non-human animal comprising no phenotype. Thus, of transgenic non-human animals generated by the method described in the Applicant's specification, the ones with the enabled use are the ones with the phenotype. As discussed in the Office Action of June 16, 2005, pages 6-11, because there is unpredictability in generating any transgenic non-human animal comprising an expected phenotype, an artisan is not enabled for the full scope of the claimed invention.

It is noted that the Examiner has reconsidered the scope of the claimed invention and enabled the invention for transgenic mice. While the invention is enabling for transgenic mice, it is not enabling for the full scope of any transgenic animal. In addition to considering whether any transgenic rats, cows, or pigs were made, one would also need to consider whether it was routine at the time of filing to make other transgenic non-human animals such as fish and frogs. At the time of filing, while the art teaches transgenic cows and pigs, the art teaches that these animals were used as bioreactors wherein a protein of interest was expressed in milk (e.g. see Velander et al., 1992, PNAS, USA, 89: 12003-12007). Unlike transgenic mice, transgenic cows and pigs had not reached the level of transgenesis, like mice, wherein transgenic mice, could comprise in their genome, heterologous promoters, including those that are tissue specific, and heterologous genes of interest. Further, as these heterologous genes were expressed in mice, transgenic mice were used as models of disease. With regards to this issue, no other animal has reached the levels of transgenesis that mice

have at the time of filing. While the Applicant has provided examples (Applicant's response, page 12) indicating other transgenic animals, it is noted that these examples are post-filing (Examiner used the filing date of patent 5,912,411, June 7, 1995, as the date at which non-human transgenic animals were contemplated.) With regards to Example h, Weinmann, this is a transgenic plant, which is unrelated to the scope of transgenic animals contemplated in the instant application. Thus, at the time of filing, while transgenic mice comprising the tet system could be obtained, the art indicates that transgenesis in other non-human animals was still in its infancy and an artisan would not have been able to obtain any transgenic non-human animals other than mouse.

With regards to the Applicant's assertion on page 11-13 of Applicant's response, point B, wherein the Applicant indicates that despite the variation in phenotypes exhibited by transgenic non-human animals associated with position effects following transgene integration, it would not be undue experimentation for an artisan to routinely screen for transgenic animals. The Examiner finds this argument persuasive and withdraws the rejection regarding this argument.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed. The rejection of claims 21-54 stands.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 24-27, 29-32 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments, page 13 of Applicant's response filed September 16, 2005, have been fully considered but they are not persuasive.

As indicated in the Office Action of June 16, 2005, "detectable levels" is a relative term and the interpretation between two artisans can differ as to what is meant as "detectable". The rejection thus stands.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21, 24-27, 29-54 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 5,912,411 for reasons of record set for in the previous Office Actions of January 16, 2004 and October 5, 2004. Although the conflicting claims are not

identical, they are not patentably distinct from each other because claims of the instant application are drawn to a transgenic non-human animal, which is broader in scope compared to the transgenic moue of the cited patent.

It is noted that in the event of the amendment of the pending claims to a transgenic mouse, the rejection will be changed to statutory double patenting rejection.

Claims 22, 23, 28, 37-54 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 5,866,755 for reasons of record set forth in the previous Office Action of January 16, 2004 and October 5, 2004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to a transgenic non-human animal, which is broader in scope compared to the transgenic moue of the cited patent.

It is noted that in the event of the amendment of the pending claims to a transgenic mouse, the rejection will be changed to statutory double patenting rejection.

It is acknowledged from the Applicant's response, April 5, 2005, that the Applicants will address these issues upon the claims being found allowable.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER